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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/485,583	02/14/00	ENDO K	ENDO=12

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EXAMINER	
STILLER,K	
ART UNIT	**PAPER NUMBER**
1617	8

DATE MAILED: 09/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/485,583	Applicant(s) ENDO ET AL.	
	Examiner Karl Stiller	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-21* is/are pending in the application.

4a) Of the above claim(s) *12-14 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of the selective iNOS inhibitor, L-N-6-(1-iminoethyl)lysine, and the bone-resorption disease to be treated, osteoporosis, in Paper No. 7, filed August 17, 2001 is acknowledged. The traversal with respect to the specie of selective iNOS inhibitor is on the ground(s) that (1) Claims 1-7 were not seen to have a lack of unity during the international stage; (2) The chain-amidine derivatives, cyclic amidine derivatives, 2-aminopyridine derivatives, and guanidine derivatives possess a single general inventive concept regardless of the differences in the structure, i.e., all of the derivatives share the common pharmacological action of inhibiting iNOS; (3) The chain-amidine derivatives, cyclic amidine derivatives, 2-aminopyridine derivatives, and guanidine derivatives do have a "common central core" which is R_1-N=C(R_2)-NH-R_3. This is not found persuasive because, with respect to item (1), Claims 1-7, pending in the international application, were cancelled by Applicant in Paper No. 4, filed February 14, 2000 prior to the restriction requirement herein. Further, please note that the international application was not prosecuted in the USA. With respect to item (2), the commonality of the pharmacological action of compounds encompassed by the claims herein is a function of the instant invention. Therefore, one of ordinary skill in the art would not have been apprised of this shared attribute. With respect to item (3), the Examiner cannot read limitations from the specification into the Claims. The Claims broadly recite "a selective iNOS inhibitor" in the methods and compositions herein. The Claims lack any defined structure for compounds encompassed by the Claims and

therefore, the moieties above cannot be seen to constitute a "common central core" shared by all compounds encompassed by the Claims. Therefore, due to the lack of an identifiable common central core, the species of
selective iNOS inhibiting compounds useful herein do not relate to a single general inventive concept under PCT Rule 13.2.

The traversal with respect to the specie of bone-resorptive disease to be treated is on the ground(s) that all diseases claimed to be treated respond to inhibiting iNOS, and therefore share a single general inventive concept. This is not found persuasive. Applicant's attention is directed to *General Electric Company v. Wabash Appliance Corporation et al* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed: "the vice of a functional Claim exists not only when a Claim is "wholly" functional, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty". Functional language at the point of novelty, as herein employed by Applicants, is further admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406: stating this usage does "little more than outlin[e] goals appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". A single general inventive concept cannot be seen on the basis that all diseases claimed to be treated respond to iNOS inhibition as discussed in the prior office action since one of skill in the art would not

recognize that diseases encompassed by the Claims are of a similar nature, e.g., have a similar pathology or respond to similar treatments.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-14, and 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected specie, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 4, filed February 14, 2000.

The Claims have been examined insofar as they read on the elected species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-11, and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over "The Pharmacological Basis of Therapeutics" in view of Hukkanen et al. and Moore et al.

"The Pharmacological Basis of Therapeutics" teaches the treatment of the elected specie of bone-resorption disease, osteoporosis, comprising the administration of various medications, including anti-resorptive agents such as calcium, estrogen, calcitonin, bisphosphonates (see p. 1540, column 2, lines 10-24, lines 38-49, p. 1541, column 1, lines 8-28, line 60 through column 2, line 2, column 2, lines 20-30, lines 31-

41). "The Pharmacological Basis of Therapeutics" also teaches that current anti-resorptive therapy acts to maintain bone mass by inhibiting resorption (see p. 1540, column 2, lines 20-26, p. 1542, column 2, lines 6-8). "The Pharmacological Basis of Therapeutics" also teaches that the method of treating osteoporosis comprising the administration of estrogen acts on bone by decreasing osteoblastic production of interleukin-6, thereby interfering with recruitment of bone-resorbing osteoclast precursors (see p. 1541, column 1, line 52 through column 2, line 6).

The primary reference does not particularly teach a kit comprising the elected specie of iNOS inhibitor, L-N-6-(1-iminoethyl)lysine, nor does it teach a method to treat osteoporosis employing the same.

Hukkanen et al. discloses that cytokines such as IL-1β induce other cytokines such as IL-6, which has already been shown to increase bone-resorption, and that this activity which leads to bone-resorption can be completely inhibited by inhibitors of NOS activity (iNOS inhibitors) (p. 5452, column 1, lines 41-48). Hukkanen et al. also disclosed that inhibitors of NOS suppress bone destruction in rat models (p. 5446, column 1, lines 20-23).

Moore et al. discloses that the elected specie of iNOS inhibitor, L-N-6-(1-iminoethyl)lysine, is a potent and selective inhibitor of iNOS (p. 3886, abstract).

It would have been obvious at the time the invention was made to modify the primary reference by employing the known selective iNOS inhibiting agent, L-N-6-(1-iminoethyl)lysine, in a method or kit to treat osteoporosis.

One of ordinary skill would have been motivated to employ L-N-6-(1-iminoethyl)lysine in a method to treat osteoporosis because "The Pharmacological Basis of Therapeutics" teaches methods of treating osteoporosis comprising the administration of bone-mass maintaining medications broadly, including estrogen, which is known to act to retard bone resorption by decreasing osteoblastic production of interleukin-6, thereby interfering with recruitment of bone-resorbing osteoclast precursors. Since Hukkanen et al. discloses that the induction of IL-6 can be completely inhibited by inhibitors of NOS activity (iNOS inhibitors) and Moore et al. discloses that the elected specie herein, L-N-6-(1-iminoethyl)lysine, is a known potent inhibitor of iNOS, one of ordinary skill would have reasonably expected this agent to be useful as anti-resorptive therapy in osteoporosis similar to the known anti-resorptive agent, estrogen.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have employed the known iNOS inhibitor, L-N-6-(1-iminoethyl)lysine, in a method to treat osteoporosis.

Note that Claims 15-18 are drawn to kits comprising the elected specie of iNOS inhibitor, L-N-6-(1-iminoethyl)lysine, and that claimed recitation of intended use of the kit, e.g., to treat the elected specie of bone resorption-associated disease, osteoporosis, to retard bone-resorption, etc., does not carry any patentable weight per se. While the Claims recite a kit, no positive recitation of the components distinguishes it over the references; therefore the kit is encompassed by the references. It is a well known

convention in the art to place known components useful in a method into a kit product for convenience and economy in practicing the method.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karl Stiller whose telephone number is 703-306-3219. The examiner can normally be reached during normal business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie can be reached at 703-308-4612. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Stiller: ks
September 4, 2001

MINNA MOEZIE, J.D.
SUPERVISORY PATENT EXAMINER
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